

University of Groningen

## What We Mean When We Talk About Adherence in Respiratory Medicine

Vrijens, Bernard; Dima, Alexandra L.; Van Ganse, Eric; van Boven, Job F. M.; Eakin, Michelle N.; Foster, Juliet M.; de Bruin, Marijn; Chisholm, Alison; Price, David

*Published in:*  
Journal of Allergy and Clinical Immunology: In Practice

*DOI:*  
[10.1016/j.jaip.2016.05.019](https://doi.org/10.1016/j.jaip.2016.05.019)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2016

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Vrijens, B., Dima, A. L., Van Ganse, E., van Boven, J. F. M., Eakin, M. N., Foster, J. M., de Bruin, M., Chisholm, A., & Price, D. (2016). What We Mean When We Talk About Adherence in Respiratory Medicine. *Journal of Allergy and Clinical Immunology: In Practice*, 4(5), 802-812.  
<https://doi.org/10.1016/j.jaip.2016.05.019>

**Copyright**

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

**Take-down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

# What We Mean When We Talk About Adherence in Respiratory Medicine



Bernard Vrijens, PhD<sup>a,b</sup>, Alexandra L. Dima, PhD<sup>c</sup>, Eric Van Ganse, MD, PhD, FRCP<sup>d,e</sup>, Job F.M. van Boven, PharmD, PhD<sup>f</sup>, Michelle N. Eakin, PhD<sup>g</sup>, Juliet M. Foster, PhD<sup>h</sup>, Marijn de Bruin, PhD<sup>c,i</sup>, Alison Chisholm, MSc<sup>j</sup>, and David Price, MD, FRCGP<sup>j,k</sup> *Visé and Liège, Belgium; Amsterdam, The Netherlands; Lyon, France; Groningen, The Netherlands; Baltimore, Md; Sydney, Australia; and Aberdeen and Cambridge, UK*

Adequate medication adherence is key for optimal benefit of pharmacological treatments. A wealth of research has been conducted to understand and identify opportunities to intervene to improve medication adherence, but variations in adherence definitions within prior research have led to ambiguity in study findings. The lack of a standard taxonomy hinders the development of cumulative science in adherence research. This article reviews the newly established Ascertaining Barriers to Compliance (ABC) taxonomy for medication adherence with a particular focus on its relevance and applicability within the context of asthma and chronic obstructive pulmonary disease management. Building on

traditional definitions and concepts within medication adherence, the ABC taxonomy considers the temporal sequence of steps a patient must undertake to be defined as “adherent to treatment”: (A) initiation, (B) implementation, and (C) persistence. We explain the clinical and research relevance of differentiating between these phases, point to differences in its applicability in observational and experimental research, review strengths and limitations of available measures, and highlight recent findings on specific determinants of these behaviors. Finally, we provide recommendations for research and practice with a view to supporting and sign posting opportunities to improve future respiratory medication adherence and

<sup>a</sup>WestRock Healthcare, Visé, Belgium

<sup>b</sup>Department of Public Health, University of Liège, Liège, Belgium

<sup>c</sup>Amsterdam School of Communication Research ASCoR, University of Amsterdam, Amsterdam, The Netherlands

<sup>d</sup>Pharmaco-Epidemiology Lyon (PEL), HESPER, Claude Bernard University, Lyon, France

<sup>e</sup>Respiratory Medicine, Croix-Rousse University Hospital, Lyon, France

<sup>f</sup>Department of Primary Care, Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

<sup>g</sup>Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University, Baltimore, Md

<sup>h</sup>Woolcock Institute of Medical Research, Clinical Management Group, University of Sydney, Sydney, Australia

<sup>i</sup>Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

<sup>j</sup>Respiratory Effectiveness Group, Cambridge, UK

<sup>k</sup>Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK

The Respiratory Effectiveness Group (REG; [www.effectivenessevaluation.org](http://www.effectivenessevaluation.org)) supported the Expert Adherence Panel Meeting at which many of the concepts presented in this paper were first discussed. REG also supported the manuscript submission costs. ALD, EvG, and MdB have received funding from the European Community's 7th Framework (FP7/2007-2013) under grant agreement no. 282593. Teva supported the meeting costs at which the concepts in this paper were discussed by the co-authors and the open access publication fee for this article. The authors had full editorial control over the ideas presented.

Conflicts of interest: B. Vrijens is a full-time employee of WestRock healthcare, the company that manufactures and commercializes the Medication Event Monitoring Systems (MEMS™). A. L. Dima has received research support from the Respiratory Effectiveness Group. E. Van Ganse is on the Pfizer board; has received consultancy fees from Steve Data/PELyon Clinical Research Organisation; has received research support from Merck, GlaxoSmithKline, ALK Abello, Bristol-Myers Squibb, and Bayer; has received lecture fees from BMS; has stock/stock options in Peylong; and has received travel support from Novartis, AstraZeneca, and Boehringer Ingelheim. J. F. M. van Boven has received travel support from the Respiratory Effectiveness Group and European Chronic Obstructive Pulmonary Disease Coalition; has received consultancy fees from AstraZeneca; and has received research support from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, and Chiesi. M. N. Eakin has received travel support from the Respiratory Effectiveness Group; has received consultancy fees from Praxis Pharmaceuticals; and has received research support

from the National Institutes of Health and the Cystic Fibrosis Foundation. J. M. Foster has received travel support from the Respiratory Effectiveness Group and European Academy of Allergy and Clinical Immunology; is on the Vertex Pharmaceuticals advisory board; and has received research support from GlaxoSmithKline and AstraZeneca. D. Price is on the boards for Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva; has received consultancy fees from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, and Teva; has received research support from UK National Health Service, British Lung Foundation, Aerocrine, AKL Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Meda, Merck, Mundipharma, Napp, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva, Zentiva; has received lecture fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, Sky-ePharma, Takeda, and Teva; has received payment for manuscript preparation from Mundipharma and Teva; has a patent with AKL Ltd; has received payment for developing educational presentations from GlaxoSmithKline and Novartis; has stock in AKL Ltd; has received travel support from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva; has received funding for patient enrolment or completion of research from Almirall, Chiesi, Teva, and Zentiva; is a peer reviewer for grant committees for Medical Research Council (2014), Efficacy and Mechanism Evaluation programme (2012), Health Technology Appraisal (2014); and owns 80% of Research in Real Life, Ltd (and its subsidiary social enterprise Optimum Patient Care), which receives unrestricted funding for investigator-initiated studies from Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, Zentiva. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 24, 2016; revised May 19, 2016; accepted for publication May 27, 2016.

Corresponding author: Bernard Vrijens, PhD, WestRock Healthcare, Rue des Cyclistes Frontière 24, Visé 4600, Belgium. E-mail: [bernard.vrijens@westrock.com](mailto:bernard.vrijens@westrock.com).

2213-2198

© 2016 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).  
<http://dx.doi.org/10.1016/j.jaip.2016.05.019>

*Abbreviations used*

ABC- Ascertaining barriers to compliance  
CMA- Continuous multiple-interval measures of medication availability  
COPD- Chronic obstructive pulmonary disease  
EMD- Electronic monitoring devices  
EMR- Electronic medical records  
FDC- Fixed dose combination  
ICS- Inhaled corticosteroids  
LABA- Long-acting  $\beta_2$ -agonists  
MPR- Medication possession ratio  
RCT- Randomized controlled trial  
TTD- Time to discontinuation

**associated research.** © 2016 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2016;4:802-12)

**Keywords:** Medication adherence; Asthma; Chronic obstructive pulmonary disease (COPD); Initiation; Implementation; Persistence; ABC taxonomy

Respiratory clinicians have access to a wide range of efficacious therapies. Randomized controlled trials (RCTs) have repeatedly demonstrated the efficacy of licensed asthma and chronic obstructive pulmonary disease (COPD) therapies in terms of their ability to minimize symptom burden, improve health-related quality of life, and maintain or slow disease progression.<sup>1,2</sup> Yet reports of numerous asthma and COPD exacerbations and related pressures on emergency and respiratory services persist.<sup>3,4</sup> This apparent disconnect is primarily explained by the gap between efficacy results derived from well-controlled, short-term RCTs involving highly selected populations and effectiveness evaluations conducted in more every day, real-life settings, typically involving diverse patient populations, across a wide range of care settings and patient characteristics and evaluated over longer time intervals than are used in RCTs.<sup>5</sup>

One of the important differentiating factors between efficacy RCTs and real-world effectiveness studies is medication adherence optimized in RCTs, but commonly suboptimal in everyday routine care. Through registration RCTs, regulatory authorities require an estimate of efficacy (or “method-effectiveness”) that assumes perfect adherence while, in practice, payers are often more interested in “use effectiveness” to inform cost-effectiveness analyses and guide market access and reimbursement decisions through pragmatic RCTs or noninterventional studies. All study designs reflect some aspect of the real world, but the ability to extrapolate the findings of registration RCTs to more routine clinical environments must be treated with caution.<sup>6</sup> The real-world implications of differences between registration RCTs and routine care adherence behaviors depend on the characteristics of both the disease and the medications as drug actions are inherently dose and time dependent. As a result, variable underdosing (which is the norm) diminishes the actions of medications in real life by various degrees compared with RCT settings.<sup>7</sup>

The importance of optimizing asthma medication in the context of routine (“real-world”) practice was recognized and stressed by the World Allergy Organization and Interasma in their joint manifesto on adherence to asthma treatment in respiratory allergy (also endorsed by Allergic Rhinitis and Its Impact on Asthma and the Global Allergy and Asthma European Network).<sup>8</sup>

The Ascertaining Barriers to Compliance (ABC) taxonomy began as an initiative of the European Union to standardize adherence-related terminology for clinical and research use.<sup>9</sup> The publication of the ABC taxonomy marked an important step forward in the standardization and future development of adherence research. To facilitate its use in respiratory research and practice, it is now important to consider its applicability and relevance to the real-life complexities of respiratory care.

Although sharing many of the common barriers to optimal adherence reported in other chronic diseases,<sup>10,11</sup> asthma and COPD stand apart because of the central role that inhaled therapy plays in their management, and the associated challenges that the effective inhaler technique presents to optimum therapy delivery and adherence.<sup>12</sup> Furthermore, the 2 conditions differ in their age of onset, pattern of symptoms, and disease course giving rise to potential differences in respective medication adherence behaviors. We consider the value of the ABC taxonomy in differentiating between adherence behaviors and clinical settings in these respiratory conditions, as a way to both understand behavior-specific determinants and establish a new standard for future respiratory adherence research. Finally, evidence gaps and unmet needs are outlined to act as a guide for future respiratory adherence researchers.

## TOWARDS A COMMON ADHERENCE TAXONOMY

On the basis of a systematic review of the medication adherence literature, Vrijens et al’s<sup>9</sup> proposed ABC taxonomy conceptualizes adherence to medications in line with principles of behavioral and pharmacological science. This proposal was developed as a response to a 2003 World Health Organization call for action to address the disease burden associated with poor medication adherence.<sup>13</sup> It also furthered the thinking laid out by the International Society for Pharmacoeconomics and Outcomes Research in their 2008 consensus statement on adherence definitions.<sup>14,15</sup>

The ABC taxonomy defines the overarching concept of “medication adherence” as the process by which patients take their medication as prescribed and subdivides it into 3 essential elements: (A) initiation; (B) implementation, and (C) persistence (see Figure 1). This subdivision outlines the sequence of events that have to occur for a patient to experience the optimal benefit from his or her prescribed treatment regimen.

Step “A” in the process, “initiation”—when the patient takes the first dose of a prescribed medication—is typically a binary event (patients either start taking their medication or not in a given time period). In contrast, step “B,” “implementation”—the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken—is a longitudinal description of patient behavior over time, that is, his or her dosing history. The final step “C,” defined within the taxonomy, “persistence,” is the time elapsed from initiation, until eventual

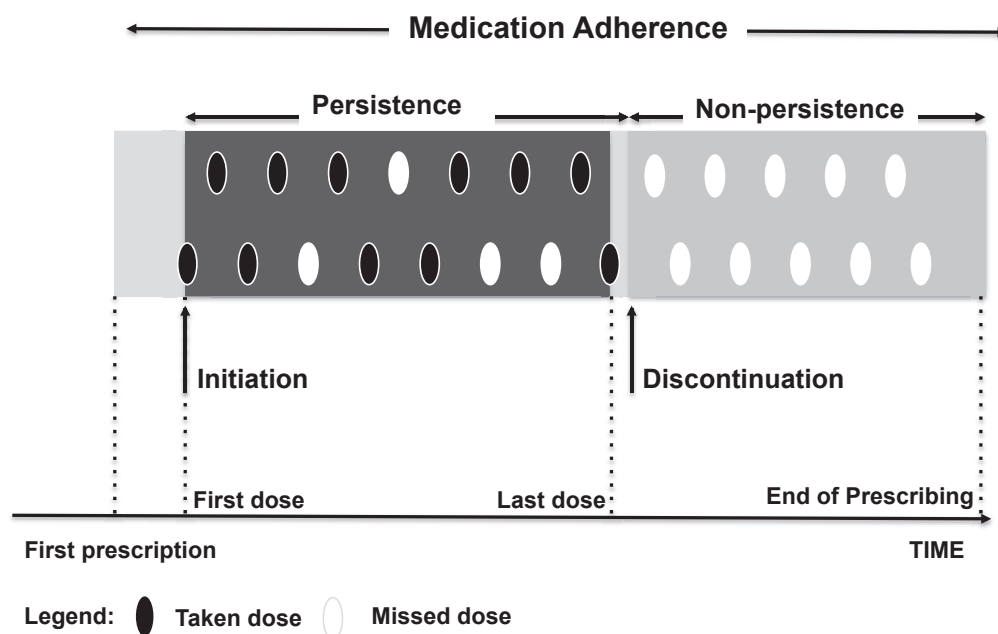


FIGURE 1. Illustration of the temporal phases of adherence outlined in the ABC taxonomy.<sup>9</sup> Adapted from Vrijens et al.<sup>9</sup>

treatment discontinuation (ie, time to event); after discontinuation, a period of nonpersistence may follow until the end of the prescribing period.

A further adherence concept, although not specifically defined in the ABC taxonomy, is that of medication “reinitiation.” The temporal steps of initiation, implementation, and persistence defined by the taxonomy, in research terms, occur (or not) in a time period in which a specific medication is prescribed for regular intake to improve health outcomes, starting with a first prescription and ending after a drug exposure period deemed sufficient for achieving the expected effect. In RCTs, this sequence maps onto the process of study participation, from study inclusion to assessment of health outcomes. Thus, initiation is by definition a single event, and nonpersistence is readily operationalized as the time interval between the last medication intake to the end of the follow-up period (and consequently depends on the length of this period).

In observational studies and clinical practice, the boundaries of this temporal sequence are less clear-cut and require additional specifications. For chronic conditions, patients can receive multiple prescriptions often over decades. Over this time interval, they may interrupt or change treatment (in consultation with the clinician or not) and they may alternate periods of substantial drug exposure with intervals without any drug exposure. Epidemiological research has employed the concepts of “treatment episodes” and “treatment gaps” to reflect such clinical realities, using time intervals for medication exposure representative of such behaviors derived from long-term patient records.<sup>16</sup> The 3 elements of the ABC taxonomy can be applied in long-term research and patient care in combination with these concepts. As such, a patient may have several treatment episodes, which may show different (re)initiation, implementation, and discontinuation values. Depending on the available data sources, the researcher or clinician may have the opportunity to assess more or less precisely these 3 elements.

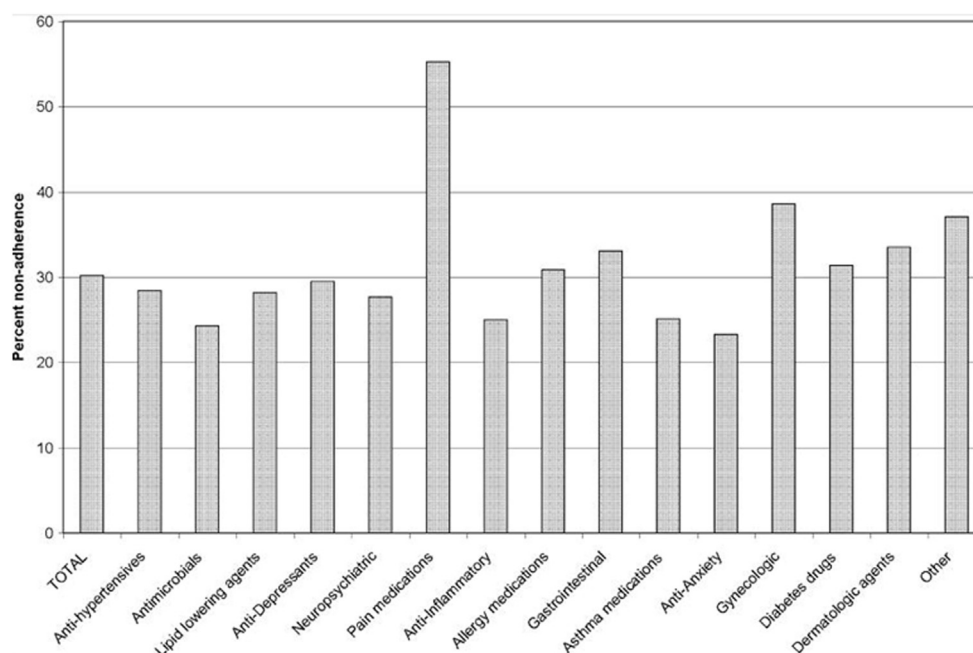
## APPLYING AND INTERPRETING THE ABC TAXONOMY IN THE CONTEXT OF ROUTINE ASTHMA AND COPD CARE

### Asthma and COPD: clinical management similarities and differences

To explore the applicability of the ABC taxonomy in the context of asthma and COPD, it is important to consider the main characteristics of 2 conditions and their management.

Asthma and COPD are both chronic obstructive lung conditions principally managed with inhaled therapies. There are 2 main categories of inhaled therapies prescribed in asthma and COPD: bronchodilators (short- or long-acting) to offer symptom relief, and anti-inflammatory therapy to target airway inflammation and minimize risk of future exacerbations (ie, acute periods of worsening).<sup>2,3</sup> Beyond these similarities in clinical presentation and therapeutic management, there are important differences between the 2 conditions that must be taken into consideration when evaluating adherence.

**COPD considerations.** COPD is characterized by fixed airflow obstruction, progressive, irreversible deterioration in lung function, older age of onset, and mediated primarily by neutrophilic inflammation.<sup>2</sup> Short- and long-acting bronchodilators, in the form of anti-muscarinics and  $\beta_2$ -agonists, are the core pillar of COPD management. Inhaled corticosteroids are often prescribed, although only licensed for use in combination with bronchodilator therapy. Other treatment options exist, such as theophylline and phosphodiesterase-4 inhibitors. As a result of the fixed airflow obstruction and progressive lung function decline over time, COPD symptoms tend to be persistent and to occur in older patients (>50 years), resulting in a need for consideration of potential comorbidities and polypharmacy factors, cognitive implications, and tailoring of inhaler device (eg, potentially avoiding those requiring strong inspiratory flow). Costello et al discuss age-related determinants of respiratory



Based on 195,930 e-prescriptions from >75,000 patients

**FIGURE 2.** Failure to initiate: primary nonadherence to newly prescribed medication (patients aged  $\geq 19$  y).<sup>16</sup> Reproduced from Fischer et al<sup>19</sup> with permission from the publisher.

medication adherence in more detail in their paper in this issue.<sup>17</sup>

**Asthma considerations.** In contrast, asthma is a variable condition (often triggered by seasonal, viral, and/or environmental exposures) with reversible airflow obstruction.<sup>1</sup> It is primarily mediated by eosinophilic inflammation and can affect patients of any age (sometimes resolving over time), presenting different management challenges (eg, in terms of inhalation technique and successful delivery) depending on the particular age group under consideration. Inhaled corticosteroids are the mainstay of anti-inflammatory controller therapy and are prescribed in combination with short- and/or long-acting bronchodilators ( $\beta_2$ -agonists) for symptom relief. Add-on therapies, such as oral steroids and/or monoclonal antibodies, are used in more severe cases. The Global Initiative for Asthma guidelines recommend a stepwise approach to management, with symptoms and risk optimized on the lowest dose of therapy appropriate, but stepped up, as required, to improve control. Use of add-on therapies (eg, theophylline and/or high-cost biologics) is recommended only in patients with severe asthma who have persistent symptoms and/or exacerbations despite optimized treatment with high-dose controller medications and treatment of modifiable risk factors. Thus, valid means of measuring and monitoring adherence are required to guide necessary therapy step-ups and, similarly, to avoid unnecessary treatment escalations.

Yet owing to the sometimes variable nature of asthma, clinician-issued prescribing instructions can vary substantially between patients. For instance, daily controller medication use may be prescribed during a specific interval each year to treat seasonal asthma. In contrast, patients with persistent asthma may

be prescribed daily controllers for long-term use, either with a fixed daily dosage or via a self-management plan, which typically specifies a fixed basis of daily controller use, rules for reliever use (eg, “as needed”), and thresholds for increased controller use.

Prescribing instructions are an important element of meaningful adherence appraisal as its evaluation requires a comparison of actual medication use against a clinically appropriate intended reference regimen. Furthermore, waxing and waning symptoms can lead to practical research challenges of differentiating between periods of episodic implementation and nonpersistence and temporary nonpersistence (and reinitiation). Therefore, disease severity, prescription recommendations, and time intervals need to be carefully considered in asthma adherence research.

## Medication initiation

**Initiation in observational studies versus RCTs.** Most treatment initiation research comes from observational studies using electronic medical records (EMRs) combined with pharmacy dispensing databases. Unlike RCTs, which typically administer the first dose on site, EMR-based studies draw on data captured within routine practice and can better reflect true initiation behaviors. However, evidence is scarce as treatment initiation is not often reported.

Indeed, a systematic review of observational evidence on medication adherence determinants in asthma, which used the ABC taxonomy to identify which of the 3 stages were investigated in the studies included, found the vast majority focused on implementation; very few considered initiation or persistence.<sup>18</sup> Yet medication initiation should never be assumed. A community-based study of initiation rates of chronic disease medications in the United States found that 20% to 30% of



**TABLE I.** Some key features, strengths, and limitations of commonly used adherence measurement methods

|                              | 1. Initiation   | 2. Implementation   | 3. Discontinuation   |
|------------------------------|---|---|--|
| <b>Routine EHR*</b>          |   |   |  |
| Granularity/Precision†       | Granularity in days, if the prescription database is also available   | Imprecise—tends to average usage of a time interval of $\geq 3$ months  | Granularity in weeks or months   |
| Validity‡                    | Relatively high (if first use follows dispensation)   | Relatively high (if standard dosing regimen or if prescription details are available)   | Relatively high (if all sources of dispensation are known)<br>Allows identification of changes in a same class of medications  |
| Ease of Access               | Few linked datasets to compare prescribed and collected medication dates  | Easy to access if available in health system  | Easy to access if available in health system   |
| <b>Patient reports</b>       |   |   |  |
| Granularity/Precision†       | Granularity in days/weeks (depends on the time window of the tool used)   | Imprecise due to recall bias  | Granularity in days/weeks (depends on patient memory)  |
| Validity‡                    | Subject to desirability bias  | Subject to desirability bias  | Subject to desirability bias   |
| Ease of Use                  | Easy to implement. May require an additional contact with the patient after prescription  | Easy to implement at point of care<br>Adds burden to the patient  | Easy to implement at point of care   |
| <b>Electronic monitoring</b> |   |   |  |
| Granularity/Precision†       | Granularity in minutes  | Granularity in minutes  | Granularity in minutes   |
| Validity‡                    | High (if first device use is followed by inhalation)  | High (especially if inhaler technique is also assessed)   | High (if medication is only used with the device)  |
| Ease of Use                  | Easy to implement in clinical trials<br>In medical practice, can be used as a good start program but requires activation and patient engagement | Easy to implement in clinical trials<br>In medical practice, can be used at specific time of care (when a problem is suspected, at treatment failure, or to support a behavioral intervention, etc.) for a defined period of time | Easy to implement in clinical trials<br>Not feasible for long-term treatments in large-scale populations—limited use due to complexity, costs, patient burden, limited availability, and fatigue |

EHR, Electronic health records.

\*Electronic Health Records, e.g. prescription (prescribing and/or dispensing) data, and health insurance (or 'claims') data.

†Granularity: the sampling rate at which it is possible to assess changes in the dynamic process of adherence (particularly relevant to objective measures); Precision: degree of reproducibility, that is, ability to measure the same value repeatedly (particularly relevant to patient reports).

‡Degree of potential systematic error in the measurement, that is, difference between the estimated and real value.

patients failed to collect their first treatment prescription.<sup>19</sup> Although asthma medications were among the higher dispensed e-prescriptions within the study, approximately one-quarter of patients prescribed new asthma therapy failed to collect their first prescription (see Figure 2).

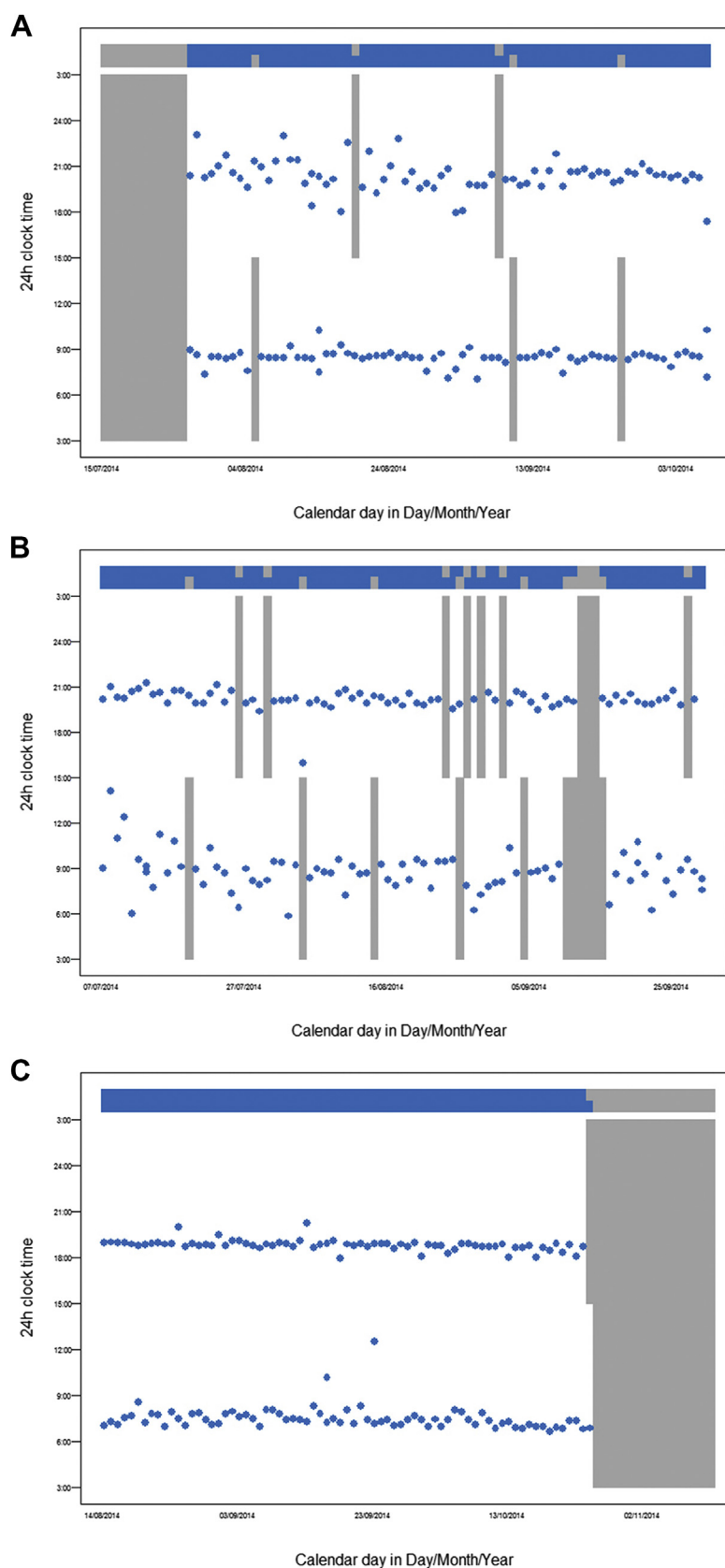
**Measurement of initiation.** Pharmacy dispensing databases provide the best source for evaluating treatment initiation behaviors in observational studies, especially when linked to clinical EMRs (eg, primary and/or secondary care prescribing data; see Table I). EMR data indicate the physician's intention that a patient should take a specific drug and pharmacy dispensing data indicate the patient's collection of the prescribed therapy—one step closer to the act of initiation. A prescription event followed by a dispensation event for the same treatment is used in research to infer therapy initiation.

Patient reports, that is, directly asking patients whether they started their prescribed treatment, provide a subjective means of assessing medication initiation. If answered truthfully, they are a direct method of assessing initiation and for capturing potential insights into the reasons and determinants of noninitiation. As with all patient reports, initiation reports will be limited by the reliability of patient responses and informed by the specificity

and appropriateness of the questions asked; careful design of assessment timing and tools can optimize the accuracy of the reports.

Electronic monitors provide an objective means by which the date of first treatment administration can be captured. Electronic monitors are the gold standard for precisely recording first treatment administration in clinical trials. In medical practice, after a prescription, the patient has to acquire the medication first and only then the electronic monitor can be activated, limiting its ability to fully capture treatment initiation in real life.

**Determinants of initiation.** In routine care, treatment initiation can be affected by a range of demographic, psychological, and practical factors, among them: denial or uncertainty of diagnosis<sup>20</sup>; lack of trust in health care professionals; medication fears; health literacy; affordability and access to therapy, age, ethnicity and sex.<sup>21,22</sup> In one study designed to evaluate determinants of initiation of asthma controller medication, for example, a higher probability of noninitiation was recorded in younger patients, female patients, those of African American ethnicity (vs white), and in those who had with fewer short-acting  $\beta_2$ -agonist refills in the preceding year.<sup>22</sup>



**FIGURE 3.** Aggregate EMR measures of implementation can result in a loss of the detail necessary to interpret and differentiate between clinically distinct implementation behaviors and between suboptimal implementation and persistence.<sup>9</sup> Examples of electronically compiled drug dosing history based on EMD in 3 patients for whom a twice-daily dosing regimen was prescribed. Dots indicate the dates

In addition, in the context of both asthma and COPD, the inhaled mode of therapy delivery can present an additional obstacle, particularly in certain age and cultural groups owing to substantial stigma around the use of medication inhalers. Research is needed to determine the extent to which stigma may prevent initiation and (if collected and administered once) subsequent implementation and persistence.<sup>22,23</sup>

**Implications for research and practice.** The limited evidence available on treatment initiation suggests that a substantial proportion of patients with chronic disease fail to implement chronic disease therapies and highlights the need for a greater focus on treatment initiation research in asthma and COPD.

## Medication Implementation

**Implementation in observational studies versus RCTs.** Interest in implementation originally stems from RCTs, where accurate estimates of drug exposure are essential for the evaluation of drug efficacy and safety. However, the highly selective inclusion criteria applied to clinical trial populations, coupled with the close monitoring, short duration, and support of correct implementation, end up reducing variation and the representativeness of RCT data with respect to real-life settings. In contrast, cohort studies that observe rather than affect clinical practice tend to include broader, more representative patient populations and explore a wider range of determinants and effects.

**Measurement of implementation.** As the more commonly studied concept within the adherence sequence,<sup>22</sup> several measures of implementation are available for research and clinical practice (see Table I). Electronic monitoring is the gold standard approach to measuring the implementation of a dosing regimen reliably and precisely (permitting granular data capture). For inhaled therapies, given the difficulty associated with the inhalation technique, electronic monitoring devices (EMDs) that have the capacity not only to record (and time/date-stamp) administration (see Figure 3), but also to capture the quality of therapy delivery (eg, inhalation technique) are preferred.<sup>24,25</sup> EMDs should be systematically used in RCTs as they provide an accurate means of evaluating drug usage and exposure.<sup>26-28</sup>

Dispensing data provide information for various algorithms estimating medication implementation, known as CMA (continuous multiple-interval measures of medication availability), MPR (medication possession ratio), or proportion of days covered. Yet although dispensing event data are often the only data source available in large-scale assessments of implementation, they lack granularity and can only generate implementation estimates over longer time intervals based on the ratio of days of medication dispensed in a given period of evaluation versus the number of days in that time period. When detailed, time-stamped EMD data can be acquired, it becomes obvious that aggregating data in CMA-like scores lead to loss of information

on distinct adherence behaviors. Figure 3 illustrates the difference between the fine-grained EMD data and aggregate implementation scores—each of the 3 patients has different clinical behaviors, but irrespective of that, all have the same average medication coverage over a 3-month time interval.<sup>9</sup> Therefore, CMA scores must be interpreted with caution and initial granularity maintained by considering shorter time intervals, to avoid further loss of information.<sup>29</sup>

Compared with objective reports, patient self-reported implementation of a dosing regimen is affected by recall bias, which limits its use in clinical research (see Table I). Several questionnaires are available, most commonly used being the Medication Adherence Report Scale<sup>30</sup> and the Morisky Medication Adherence Scale.<sup>31</sup> Although subject to potential recall bias, the quality of patient-reported implementation can be improved by intelligent questionnaire design that, for instance, uses clearly defined terms, facilitates recall and response, and normalizes nonadherence. In medical practice, patient (self-) reports of nonadherence are the most cost-effective method of adherence monitoring available. Self-report questionnaires can provide valuable information for research and clinical practice, particularly when linked with EMD, prescribing, or dispensing data.<sup>32</sup>

**Determinants of implementation.** Each person's willingness and ability to implement therapy as prescribed may be influenced by personal characteristics, lifestyle factors, attitudes, beliefs, skills, and by his or her ability to make a habit out of medication taking and build it into his or her daily routine. A wide range of factors—social and economic, health care team and system-related, disease-related, therapy-related, and patient-related (see later papers in this issue by van Boven et al, Braido et al, and Costello et al)—have all been shown to play a part in the successful implementation of asthma and COPD medications.<sup>33</sup>

For example, a recent pharmacy-based asthma study explored the frequency and drivers of patients' spontaneously changing inhaled corticosteroid (ICS) dose. The authors found that 21% of patients had spontaneously changed the dose over the last 3 months and that patient perception of asthma as a concern in their life was the characteristic most strongly associated with changing doses.<sup>34</sup> In an Australian study, which used electronic monitoring to measure adherence to fixed combination therapy in adults with asthma, barriers to implementation included concern about, or experience of, side effects while facilitators to implementation included the belief that asthma is a long-term condition, the belief that treatment is necessary to keep asthma under control, being willing to (try) to take treatment every day, and having a medication-taking routine in place.<sup>35</sup>

In COPD, a study of implementation and its correlates in Global Initiative for Chronic Obstructive Lung Disease stages II-IV, patients were asked to self-report (via questionnaire) their implementation of respiratory drugs (over the past 3 months) and their perception of therapy.<sup>36</sup> A total of 45% of the respondents admitted to having forgotten their respiratory

---

and times of drug intake. Bars indicate missed doses. **A**, Patient with late initiation but good implementation. **B**, Patient with suboptimal implementation (missed single and consecutive doses, large variability in timing of drug intakes). **C**, Patient with excellent implementation but short persistence (early discontinuation). EMD, Electronic monitoring devices; EMR, electronic medical records. (Adapted with permission from Vrijens B, De Geest S, Huges DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691-705.<sup>9</sup>)



therapy, whereas 30% interrupted it in the absence of any perceived benefit. Risks of accidental omissions were significantly higher in patients who complained about having too many medications to take on a daily basis and among current smokers. Women were more likely to interrupt therapy intentionally.

In asthma and COPD, assessment of medication implementation is also subject to patients' ability to master (and maintain mastery of) their prescribed inhaler device(s). Challenges introduced by inhaled medications can include a combination of delivery issues (eg, knowing the sequence of steps required to use the inhaler correctly, successful dose preparation [eg, insertion of a tablet into an inhaler; inhaler positioning], inspiratory flow rate, and in pressurized metered-dose inhalers, dose actuation and coordination with breath inhalation); practical issues (eg, integration and scheduling with coexisting medications, storage, and device cleaning); and psychosocial challenges (eg, self-consciousness about inhaler use in public).<sup>37,38</sup> These issues are discussed in detail elsewhere in this issue: Braido et al.<sup>39</sup>

**Implications for research and practice.** In summary, adherence studies need to be thoughtfully designed to target implementation specifically, using EMDs as the first choice assessment method where possible or, linked dispensing and patient reports (as relevant). There remain practical barriers to the optimum integration of EMDs into current clinical practice, among them: patient mistrust, complexities and/or burden of use, device failures, and, importantly, cost. Wider uptake of available devices may address some of these challenges through reduction in unit cost, improved usability (facilitated by broader user feedback), and exposure and/or familiarity to devices (eg, EMD integration into smartphones) countering any initial skepticism toward digital innovations. Irrespective of the method of evaluation chosen, clear justification and documentation of the chosen approach (questionnaire/computation) should be provided to enable meaningful interpretation and reproducibility of the results.

## Medication persistence and discontinuation

**Persistence in observational studies versus RCTs.** The concept of treatment persistence is ostensibly a research construct, traditionally used in epidemiology (in relation to cohort studies) and often overlooked in RCTs. It is used to infer the degree of acceptability and/or patient satisfaction with a prescribed treatment regimen, that is, the patient's willingness and/or ability to implement over a predefined follow-up period; nonpersistence will be censored if treatment discontinuation is not observed during the defined period of follow-up.

Although in RCTs early discontinuation is relevant for estimates of treatment efficacy and satisfaction over relatively short time periods, observational studies provide complementary information on time to treatment discontinuation in routine care over the longer term (within treatment episodes that need careful definition).

**Measurement of persistence.** Treatment discontinuation can be assessed using EMDs, self-report (by asking patients about their current use, or time of discontinuation), and dispensing data (see Table I).

Within the routine care setting, dispensing and/or refill records are the gold standard for persistence evaluations and have

been the main source of data for persistence studies to date. Yet they are not without limitations, particularly in terms of the granularity—the sampling rate at which it is possible to assess changes in the dynamic process of implementation and persistence (see Table I). Dispensing and/or refill records are, for example, unable to differentiate between the moment of discontinuation and the end of a treatment episode, potentially defining any gap in treatment as nonpersistence. The concept of a treatment gap (time between date of last prescription issued in a given treatment episode and date of the following prescription, if available) is used to differentiate between implementation and nonpersistence across chronic disease adherence research, typically defining nonpersistence as discontinuation of the therapy class after a prespecified permitted gap between refills (eg, 30-, 60-, and 90-day refill gaps, depending on the average prescription duration).<sup>16,40,41</sup> Although this concept has sound clinical rationale for conditions with consistent symptoms or a progressive disease course (eg, COPD), the common use of self-management plans and/or as-needed therapy in mild asthma and episodic use in seasonal disease present real challenges for asthma adherence research and more accurate methods need to be developed for assessing discontinuation, ideally using multiple data sources.

Electronic monitoring devices offer a means of more intensive objective monitoring of adherence behaviors—identifying the exact date and/or time of first, subsequent, and final drug administrations (see Table I). They are a valuable tool in niche routine care settings where close adherence monitoring is required, for example, severe asthma services, and are the gold standard for monitoring drug exposure and discontinuation (and comparisons with patient-reported measures).

**Determinants of persistence.** In routine care, persistence to maintenance asthma and COPD medication is often poor and differs between the 2 conditions. An EMR study that evaluated persistence (ie, time to discontinuation, TTD) across 5 classes of asthma and COPD therapies (ICS, ICS/long-acting  $\beta_2$ -agonists [LABA], long-acting muscarinic antagonists, and theophylline) found significantly longer TTD for patients with physician-diagnosed COPD compared with asthma.<sup>42</sup> Although patients with COPD in the study displayed both higher implementation (defined by MPR) and greater TTD than patients with asthma, the likelihood of persistence at 1 year was similar for both patient populations.

In COPD, studies have shown an association between nonpersistence to tiotropium and a number of factors.<sup>43</sup> For example, a retrospective study of persistence with tiotropium in a Japanese population with COPD found the following patient characteristics to be predictors of discontinuation within the first year of drug therapy: young age, current smoking status, less severe disease, and absence of respiratory symptom alleviation.<sup>44</sup> Some of these associations bore out in a similarly designed French EMR study. Of the 1147 newly treated patients, 64% persisted with tiotropium over a 12-month period. Discontinuation rates were lower in patients with more severe disease, when at least two other respiratory drugs were co-prescribed and/or if treatment was initiated by a private sector specialist or hospital physician. Age and gender did not appear to have any clear effect on discontinuation rates.<sup>45</sup>

Other treatment-level determinants can also play a role in early discontinuation. A negative association has been shown

**TABLE II.** Recommendations for asthma and COPD medication adherence research and clinical assessment in the context of the ABC conceptualization of adherence steps

| Topic         | Initiation  | Implementation   | Discontinuation  |
|---------------|---|--|--|
| Prevalence    | <ul style="list-style-type: none"> <li>Quantify the extent of medication noninitiation in everyday routine care, across a range of health care systems/settings</li> </ul>  | <ul style="list-style-type: none"> <li>Quantify the prevalence and characterize the nature of implementation behaviors by targeted evaluations (separate to initiation and persistence assessments) and in both experimental (via RCTs) and real-life (via observational studies) settings</li> </ul>  | <ul style="list-style-type: none"> <li>Quantify medication persistence rates over a range of:               <ul style="list-style-type: none"> <li>Time periods</li> <li>Disease states</li> <li>Health care systems/settings</li> </ul> </li> </ul>   |
| Measurement   | <ul style="list-style-type: none"> <li>Integrate EMRs (eg, prescribing and dispensing records <math>\pm</math> EMD data) to provide a more complete picture of medication initiation, both initiation occurrence and time to initiation</li> <li>Refine of initiation patient reports: use of appropriate wording and question timing to capture accurate patient data</li> </ul> | <ul style="list-style-type: none"> <li>Use EMD data to assess implementation where study settings and resources permit</li> <li>Document and justify the choice of measurement tools to enable meaningful interpretation and reproducibility</li> <li>For working with dispensing data: develop (and apply) standardized methodologies to:               <ul style="list-style-type: none"> <li>Differentiate accurately between implementation and persistence behaviors</li> <li>Retain maximum data granularity and clinical meaning</li> </ul> </li> <li>Optimize reliability of implementation self-reports by careful question design (ie, improve report accuracy) and linkage with other data sources</li> </ul> | <ul style="list-style-type: none"> <li>Use EMD data and/or linked data sources to improve the accuracy of nonpersistence assessments</li> <li>For working with dispensing data:               <ul style="list-style-type: none"> <li>Develop (and apply) standardized methodologies to differentiate accurately between implementation and persistence behaviors (draw on real-world seasonal and self-management prescribing and dose adjustment patterns)</li> <li>Define appropriate treatment gaps for different clinical scenarios (eg, for different: levels of disease severity and symptom profiles—variable vs persistent)</li> </ul> </li> </ul> |
| Determinants  | <ul style="list-style-type: none"> <li>Explore risk factors for noninitiation (eg, sociodemographics, disease stage)</li> <li>Identify modifiable determinants of noninitiation (eg, beliefs about illness and treatment, stigma perceptions)</li> </ul>  | <ul style="list-style-type: none"> <li>Improve agreement implementation determinant definitions</li> <li>Develop standardized model methodologies for evaluating implementation determinants</li> </ul>  | <ul style="list-style-type: none"> <li>Characterize determinants of non-persistence to:               <ul style="list-style-type: none"> <li>Enable early identification</li> <li>Target interventions</li> </ul> </li> </ul>  |
| Consequences  | <ul style="list-style-type: none"> <li>Evaluate the specific effects of non- or delayed medication initiation on clinical outcomes</li> </ul>   | <ul style="list-style-type: none"> <li>Explore the time-varying nature of implementation on health outcomes (eg, via longitudinal study designs)</li> </ul>  | <ul style="list-style-type: none"> <li>Evaluate the time sequence of adherence behaviors and outcomes to determine causality</li> </ul>  |
| Interventions | <ul style="list-style-type: none"> <li>In clinical practice: improve timely assessment of medication initiation (and/or barriers to) to inform interventions</li> </ul>   | <ul style="list-style-type: none"> <li>Identify target patient groups for EMD use</li> <li>Explore moderators of implementation intervention effectiveness</li> <li>In clinical practice: combine clinician-delivered patient support with EMDs (as appropriate and available) to improve implementation</li> </ul>  | <ul style="list-style-type: none"> <li>In clinical practice: enquire specifically about treatment discontinuation (and its causes) in an empathic manner to inform targeting of interventions and support treatment reinitiation</li> </ul>  |

ABC, Ascertaining barriers to compliance; COPD, chronic obstructive pulmonary disease; EMD, electronic monitoring devices; EMR, electronic medical records; RCT, randomized controlled trial.

between the number of inhalers prescribed (for different medications) and persistence—patients with COPD prescribed multiple ( $\geq 2$ ) long-acting inhaled therapies have been shown to have a 40% higher treatment discontinuation rate than patients taking a single long-acting inhaled drug.<sup>46</sup> Differential 12-month persistence rates have also been demonstrated to different COPD therapies, with tiotropium monotherapy associated with higher persistence rates than guideline-recommended alternatives.<sup>45,47</sup>

In asthma, a dispensing records study of persistence to fixed dose combination (FDC) maintenance therapy found that, on average, more than half the patients ( $n = 5504$ ) filled a 30-day prescription only once over the 1-year interval. Higher persistence was associated with being male, being older than 35 years,

having a comorbid disorder, having a lower monetary value copay (\$1.01 vs \$10), previous bronchodilator use, and a prescription for higher dose maintenance therapy. The authors concluded that most adult patients with asthma taking FDC controller therapy obtained a single fill before abandoning their controller medication and called for a reappraisal of current treatment guidelines and educational strategies for both providers and patients.<sup>48</sup> However, appropriate prescribing must be determined to enable correct measurement of persistence rates.<sup>49</sup>

Other controller therapy persistence studies involving adult patients with asthma have reported persistence rates of  $\leq 15\%$  at 12 months in patients prescribed fixed dose combination ICS/LABA and  $\leq 10\%$  in those on ICS/LABA as separate inhalers, or ICS alone.<sup>50,51</sup> Persistence rates in the 2 studies appeared to be

largely related to patient factors (eg, disease severity) and to treatment-related factors (eg, daily dosing frequency).

**Implications for research and practice.** Although somewhat conceptual and arbitrarily modifiable by the duration of the defined outcome period, the concept of treatment discontinuation does hold clinical value.

Interpretation of persistence requires the development of a consensus definition of a clinically meaningful treatment gap (particularly in variable conditions such as asthma) to help differentiate between treatment holidays, flexibility of dosing regimen, and true nonpersistence.

In clinical practice, if a clinician suspects, or if a patient reports, no recent medication use, it is important to understand whether it is a case of true discontinuation or possible suboptimal implementation and then to investigate and address possible causes of discontinuation. Use of nonjudgmental and empathic language and/or tone is recommended to encourage patients to disclose their adherence decisions. The assessment of persistence is critical to interpreting the patient's clinical scenario and medication needs and key to preventing unnecessary escalation of therapy and associated health care costs (as discussed further by van Boven et al in their paper in this issue).<sup>52</sup>

## CONCLUSIONS

The ABC taxonomy proposes that the ultimate goal of adherence management is “to achieve and maintain the best use, by patients, of appropriately prescribed medicines in order to maximize benefit and minimize the risk of harm.”<sup>9</sup> Development of the taxonomy has been an important step toward efficient medication adherence research. Subdividing the hitherto single act of medication adherence into discrete concepts of (A) initiation, (B) implementation, and (C) persistence helps to focus research questions and identify measures and corresponding data sources to answer them. Better characterization and consideration of the determinants of associated behaviors will help guide clinical use of available adherence interventions to maximize potential benefit, minimize potential risk, and avoid unnecessary treatment escalation (see the paper by Dima et al in this issue).<sup>53</sup>

The ABC taxonomy has broad relevance across all medical conditions, and its adoption is critical to improving clinical understanding of patients' adherence behaviors and to setting new standards for adherence research. However, it must be interpreted and applied in the context of the specific characteristics of the condition under consideration. In asthma and COPD, the inhaled route of therapy delivery is central, in particular, for its potential capacity to affect all steps of the adherence pathway negatively. Furthermore, the cyclic and often seasonal nature of respiratory symptoms seen in asthma often complicates medication adherence due to flexible dosage recommendations in self-management plans.

From an evidence synthesis and research efficiency perspective, future success of the ABC taxonomy within asthma and COPD requires investigators to address unmet research needs (see Table II) through consistent use (and clear documentation of use) of the proposed terminology and recognized evaluation measures. All measures have limitations (see Table I for a comparative overview of their characteristics). Dispensing data are unable to capture more granular fluctuations in adherence behaviors. The accuracy of self-reports varies substantially

depending on questionnaire design decisions that can limit or improve the respondent's ability to accurately remember and report on their behaviour.<sup>54,55</sup> The use of EMD data is not only limited by a number of practical issues (eg, device failure, complexity, mistrust of technologies, expense), but also by the availability of only relatively small-scale, short-term data collection due to practical constraints. Where feasible, linkage of multiple data sources enables richer explorations of patient behaviors, validation of existing measures, and improved clinical interpretation. Therefore, generating robust research evidence requires thoughtful selection of the best assessment approaches available for the specific aspect of adherence and particular research question under consideration and clear reporting of the research question(s), assessment method(s), results and specific implications, and relevant context. Within the clinical setting, reviewing a combination of refill history, self-report, and EMD data can help the health care professional understand the contribution of adherence behaviors to the patient's health status. Access to such data provides a starting point for discussing potential barriers to medication use, and by selecting the optimum measurement-guided management approach, through a process of shared-decision making,<sup>56</sup> patient empowerment is appropriately placed at the heart of good clinical care.

## REFERENCES

1. Global Initiative for Asthma. GINA Report, Global Strategy for Asthma Management and Prevention; 2014. Available from: <http://ginasthma.org/>. Accessed December 28, 2015.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management, and Prevention of COPD; 2016. Available from: <http://goldcopd.org/>. Accessed December 28, 2015.
3. The Global Asthma Network. The Global Asthma Report 2014. Auckland, New Zealand: Global Asthma Network; 2014.
4. Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clinicoecon Outcomes Res* 2013;5:235-45.
5. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol* 2012;52:275-301.
6. Roche N, Reddel HK, Agusti A, Bateman ED, Krishnan JA, Martin RJ, et al. Integrating real-life studies in the global therapeutic research framework. *Lancet Respir Med* 2013;1:e29-30.
7. Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. *Clin Pharmacol Ther* 2014;95:617-26.
8. World Health Organization. Manifesto on Adherence to Asthma Treatment in Respiratory Allergy. Available from: [http://www.worldallergy.org/UserFiles/file/GWCManifestoAdherenceChicago\\_fullpage.pdf](http://www.worldallergy.org/UserFiles/file/GWCManifestoAdherenceChicago_fullpage.pdf). Accessed December 28, 2015.
9. Vrijens B, De Geest S, Huges DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691-705.
10. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Curr Med Res Opin* 2009;25:2303-10.
11. Center for Health Policy Research. Adherence to HIV Therapy: Building a Bridge to Success Forum for Collaborative HIV Research. Washington, DC: George Washington University Medical Center; 1999.
12. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011;105:930-8.
13. World Health Organization. Adherence to Long-Term Therapies—Evidence for Action; 2003. Available from: <http://apps.who.int/medicinedocs/pdf/s4883e/s4883e.pdf>. Accessed October 21, 2015.
14. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. *Value Health* 2008;11:44-7.

15. Hutchins DS, Zeber JE, Roberts CS, Williams AF, Manias E, Peterson AM, IPSOR Medication Adherence and Persistence Special Interest Group. Initial medication adherence-review and recommendations for good practices in outcomes research: an ISPOR medication adherence and persistence special interest group report. *Value Health* 2015;18:690-9.
16. Gardarsdottir H, Souverein PC, Egberts TC, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. *J Clin Epidemiol* 2010;63:422-7.
17. Costello RW, Foster JM, Grigg J, Eakin MN, Canonica W, Yunus F, et al. Seven stages of man—the role of age and cognition on medication adherence. *J Allergy Clin Immunol Pract* 2016.
18. Dima AL, Hernandez G, Cunillera O, Ferrer M, de Bruin M. ASTRO-LAB group. Asthma inhaler adherence determinants in adults: systematic review of observational data. *Eur Respir J* 2015;45:994-1018.
19. Fischer MA, Stedman MR, Lii J, Vogeli C, Shrank WH, Brookhart MA, et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. *J Gen Intern Med* 2010;25:284-90.
20. Barr RG, Celli BR, Martinez FJ, Ries AL, Rennard SI, Reilly JJ Jr, et al. Physician and patient perceptions in COPD: the COPD Resource Network Needs Assessment Survey. *Am J Med* 2005;118:1415.
21. Restrepo RD, Alvarez MT, Wittebel LD, Sorenson H, Wettstein R, Vines DL, et al. Medication adherence issues in patients treated for COPD. *Int J Chron Obstruct Pulmon Dis* 2008;3:371-84.
22. Cole S, Seale C, Griffiths C. 'The blue one takes a battering': why do young adults with asthma overuse bronchodilator inhalers? A qualitative study. *BMJ Open* 2013;3:e002247.
23. Price D, David-Wang A, Ho JC-M, Jeong JW, Liam CK, Lin J, et al, REALISE Asia Working Group. Time for a new language for asthma control: results from REALISE Asia. *J Asthma Allergy* 2015;8:93-103.
24. D'Arcy S, MacHale E, Seheult J, Holmes MS, Hughes C, Sulaiman I, et al. A method to assess adherence in inhaler use through analysis of acoustic recordings of inhaler events. *PLoS One* 2014;9:e98701.
25. Van Boven, Trappenburg JC, van der Molen T, Chavannes NH. Towards tailored and targeted adherence assessment to optimise asthma management. *NPJ Prim Care Respir Med* 2015;25:15046.
26. Nides M, Tashkin DP, Simmons MS, Wise R, Li VC, Rand CS. Improving inhaler adherence in a clinical trial through the use of the nebulizer chronolog. *Chest* 1993;104:501-7.
27. Bender B, Wamboldt FS, O'Connor SL, Rand C, Szefer S, Milgrom H, et al. Measurement of children's asthma medication adherence by self-report, mother report, canister weight, and Doser CT. *Ann Allergy Asthma Immunol* 2000;85:416-21.
28. Simmons MS, Nides MA, Rand CS, Wise RA, Tashkin DP. Unpredictability of deception in compliance with physician-prescribed bronchodilator inhaler use in a clinical trial. *Chest* 2000;118:290-5.
29. Dima A, Souverein P, Koster P, Chisholm A, Price D, Colice G. REG study: real-life, longitudinal ICS adherence patterns in a UK asthma population. *Eur Respir J* 2015;46(Suppl 59):1238.
30. Horne R, Weinman J. Self-regulation and self-management in asthma: exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. *Psychol Health* 2002;17:17-32.
31. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;24:67-74.
32. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med* 2015;5:470-82.
33. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. *Pharm Med Outcomes Res* 2013;4:91.
34. Laforest L, Van Ganse E, Devouassoux G, Chatté G, Tamberou C, Belhassen M, et al. Deliberate interruptions and changes of dose of inhaled corticosteroids by asthma patients: "a community pharmacy study". *Rev Mal Respir* 2015;32:8-17.
35. Foster JM, Smith L, Bosnic-Anticevich SZ, Usherwood T, Sawyer SM, Rand CS, et al. Identifying patient-specific beliefs and behaviours for conversations about adherence in asthma. *Intern Med J* 2012;42:e136-44.
36. Laforest L, Denis F, Van Ganse E, Ritleng C, Saussier C, Passante N, et al. Correlates of adherence to respiratory drugs in COPD patients. *Prim Care Respir J* 2010;19:148-54.
37. Westerik JA, Carter V, Chrystyn H, Burden A, Thompson SL, Ryan D, et al. Characteristics of patients making serious inhaler errors with a dry powder inhaler and association with asthma-related events in a primary care setting. *J Asthma* 2016;53:231-9.
38. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J* 2002;19:246-51.
39. Braido F, Chrystyn H, Baiardini I, Bosnic-Anticevich S, van der Molen T, Dandurand RJ, et al. "Trying, But failing" - the role of inhaler technique and mode of delivery in respiratory medication adherence. *J Allergy Clin Immunol Pract* 2016;4:823-32.
40. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. *J Manag Care Pharm* 2009;15:728-40.
41. Steinberg SC, Faris RJ, Chang CF, Chan A, Tankersley MA. Impact of adherence to interferons in the treatment of multiple sclerosis: a non-experimental, retrospective, cohort study. *Clin Drug Investig* 2010;30:89-100.
42. Covvey JR, Mullen AB, Ryan M, Steinke DT, Johnston BF, Wood FT, et al. A comparison of medication adherence/persistence for asthma and chronic obstructive pulmonary disease in the United Kingdom. *Int J Clin Pract* 2014;68:1200-8.
43. Bereznicki BJ, Peterson GM, Jackson SL, Walters H, Hardley FL, Gavagna GA, et al. Describing drivers of and barriers to persistence with tiotropium in patients with chronic obstructive pulmonary disease: a mixed-methods approach. *Int J Pharm Pract* 2015;23:154-7.
44. Tanaka K, Kamiishi N, Miyata J, Kabata H, Masaki K, Ogura-Tomomatsu H, et al. Determinants of long-term persistence with tiotropium bromide for chronic obstructive pulmonary disease. *COPD* 2015;12:233-9.
45. Laforest L, Licaj I, Devouassoux G, Hartwig S, Marvalin S, Van Ganse E. Factors associated with early adherence to tiotropium in chronic obstructive pulmonary disease. *Chron Respir Dis* 2013;10:11-8.
46. Yu AP, Guérin A, Ponce de Leon D, Ramakrishnan K, Wu EQ, Mocarski M, et al. Therapy persistence and adherence in patients with chronic obstructive pulmonary disease: multiple versus single long-acting maintenance inhalers. *J Med Econ* 2011;14:486-96.
47. Cramer JA, Bradley-Kennedy C, Scalera A. Treatment persistence and compliance with medications for chronic obstructive pulmonary disease. *Can Respir J* 2007;14:25-9.
48. Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol* 2006;118:899-904.
49. Poulos LM, Ampon RD, Marks GB, Reddel HK. Inappropriate prescribing of inhaled corticosteroids: are they being prescribed for respiratory tract infections? A retrospective cohort study. *Prim Care Respir J* 2013;22:201-8.
50. Marceau C, Lemièrre C, Berbiche D, Perreault S, Blais L. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. *J Allergy Clin Immunol* 2006;118:574-81.
51. Breekveldt-Postma NS, Koerselman J, Erkens JA, van der Molen T, Lammers WJ, Herings RMC. Treatment with inhaled corticosteroids in asthma is too often discontinued. *Pharmacoepidemiol Drug Saf* 2008;17:411-22.
52. van Boven JFM, Ryan D, Eakin MN, Canonica GW, Barot A, Foster JM, et al. Enhancing respiratory medication adherence: the role of health care professionals and cost-effectiveness considerations. *J Allergy Clin Immunol Pract* 2016;4:835-46.
53. Dima AL, de Bruin M, Van Ganse E, ASTRO-LAB group. Mapping the asthma care process: implications for research and practice. *J Allergy Clin Immunol Pract* 2016;4:868-76.
54. Alili ME, Vrijens B, Demonceau J, Evers SM, Hilgsmann M. A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. *Br J Clin Pharmacol* 2016;82:268-79.
55. Tourangeau R, Rips LJ, Rasinski K. The Psychology of Survey Response. Cambridge, United Kingdom: Cambridge University Press; 2000.
56. Charles C, Gafni A, Whelan T. Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making. *Soc Sci Med* 1999;49:651-61.